Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

THE FOOD AND DRUG ADMINISTRATION NEEDS TO IMPROVE THE PREMARKET TOBACCO APPLICATION REVIEW PROCESS FOR ELECTRONIC NICOTINE DELIVERY SYSTEMS TO PROTECT PUBLIC HEALTH

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Office of Inspector General

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Report in Brief
Date: November 2023
Report No. A-06-22-01002

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
OFFICE OF INSPECTOR GENERAL

The Food and Drug Administration Needs To Improve the Premarket Tobacco Application Review Process for Electronic Nicotine Delivery Systems To Protect Public Health

Why OIG Did This Audit

Use of e-cigarettes by youth remains a public health issue that is affecting children, families, schools, and communities. In July of 2019, a U.S. District court issued an order directing the Food and Drug Administration (FDA) to require that premarket tobacco product applications (PMTAs) be submitted for all new deemed tobacco products; otherwise, they are subject to the FDA's enforcement actions. By the September 9, 2020, deadline, FDA's Center for Tobacco Products (CTP) received PMTAs for more than 6 million electronic nicotine delivery systems (ENDS) products.

Our objectives were to determine (1) FDA's progress on reviewing applications for ENDS products; (2) whether FDA followed Federal statutes, regulations, policies, and guidance when granting or denying ENDS products; and (3) what actions FDA has taken to ensure that ENDS products that are not appropriate for the protection of public health are kept off the market.

How OIG Did This Audit

Our audit covered the PMTAs submitted to CTP from August 1, 2019, through September 9, 2020. To accomplish our audit objectives, we reviewed applicable Federal and program requirements, interviewed CTP officials, and reviewed the submission documents and CTP work products of a judgmental sample of ENDS products for which a PMTA was submitted.

What OIG Found

FDA's CTP made progress in reviewing PMTAs for ENDS products submitted by September 9, 2020. However, CTP was unable to complete a review of all the submitted PMTAs within the 1-year period during which, in accordance with a court order, products with applications filed in a timely manner might remain on the market pending CTP review. As of October 19, 2022, CTP had yet to decide on 53,128 of nearly 6.7 million ENDS products for which it received an application during the audit period.

CTP generally followed Federal statutes, regulations, policies and procedures, and guidance when granting or denying marketing orders for ENDS products; however, for the 15 products OIG reviewed that received a marketing-granted order, CTP did not issue an order within the 180 days. Even though CTP had outlined a timeline to meet the 180-day deadline, it encountered delays and was unable to comply.

CTP conducted enforcement actions, such as sending warning letters and seeking injunctions, to ensure that ENDS products that were not appropriate for the protection of public health were not marketed. As of October 2022, more than 440 warning letters had been issued to firms marketing illegal e-cigarettes containing tobacco-derived nicotine. Additionally, the Department of Justice, on FDA's behalf, filed the first complaints for permanent injunctions in Federal district courts against six e-cigarette manufacturers that failed to submit PMTA's for their products.

What OIG Recommends and FDA Comments

We recommend that CTP work with the Office of Personnel Management (OPM) to obtain direct-hire authority to assist CTP in reaching its full-time equivalent personnel goal and assess the PMTA review process and develop an action plan to resolve the backlog of PMTA applications and achieve compliance with the 180-day statutory timeline.

In written comments on our draft report and commenting on behalf of CTP, FDA concurred with the two recommendations and described actions it has taken or plans to take to address the findings. FDA stated that HHS, on behalf of CTP, submitted a new request to OPM for direct hire authority and CTP has begun work on an action plan to resolve the backlog of PMTA applications.

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INTRODUCTION

WHY WE DID THIS AUDIT

Use of e-cigarettes by youth remains a public health issue that is affecting children, families, schools, and communities. Results from the 2022 National Youth Tobacco Survey (NYTS) show that a disturbing number of youths use e-cigarettes, a type of electronic nicotine delivery system (ENDS), on a regular basis. The survey found that 14.1 percent of high school students and 3.3 percent of middle school students reported current e-cigarette use; among high school e-cigarette users, 46 percent are using on 20 or more days of the month, and 30 percent of them use e-cigarettes every day. Middle schoolers also show signs of strong nicotine dependence, with a fifth of middle school users using e-cigarettes on 20 or more days in a month and nearly 12 percent of them using daily. Among youth e-cigarette users overall, almost 85 percent use flavored e-cigarettes.[1]

On July 12, 2019, the U.S. District Court for the District of Maryland issued an order directing the Food and Drug Administration (FDA) to require that premarket tobacco applications (PMTAs) for all new deemed tobacco products be submitted to the agency by May 12, 2020, and provided a 1-year period for products with applications filed in a timely manner to remain on the market pending FDA review of the applications.[2, 3] On April 22, 2020, the court granted a 120-day extension due to the coronavirus public health emergency, which means that for deemed new tobacco products on the market as of August 8, 2016, PMTAs must be filed by September 9, 2020; otherwise, they are subject to FDA enforcement actions. By the September 9, 2020, deadline, FDA's Center for Tobacco Products (CTP) received PMTAs for more than 6 million ENDS products.

OBJECTIVES

Our objectives were to determine (1) FDA's progress on reviewing PMTAs for ENDS products; (2) whether FDA followed Federal statutes, regulations, policies, and guidance when granting or denying ENDS products; and (3) what actions FDA has taken to ensure that ENDS products that are not appropriate for the protection of public health are kept off the market.

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[1] Centers for Disease Control and Prevention, "E-cigarette Use Among Middle and High School Students — United States, 2022." Available online at Notes from the Field: E-cigarette Use Among Middle and High School Students — United States, 2022 (cdc.gov). Accessed on July 18, 2023.

[2] Section 910(a)(1) of the Federal Food, Drug and Cosmetic Act (FD&C Act) defines a new tobacco product as any tobacco product that was not commercially marketed in the United States as of Feb. 15, 2007, or any modification of a tobacco product for which the modified product was commercially marketed in the United States after Feb. 15, 2007.

[3] *American Academy of Pediatrics v. Food and Drug Administration,* 399 F. Supp. 3d 479, 481 (D. Md. 2019).

BACKGROUND

FDA's Oversight of Tobacco Products

FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices, and by ensuring the safety of our Nation's food supply, cosmetics, and products that emit radiation.

In 2009, the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) was enacted, granting FDA the authority to regulate the manufacture, marketing, and distribution of cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco products to protect the public health and reduce tobacco use by minors (P.L. No. 111-31). The Tobacco Control Act also gave FDA the authority to issue regulations deeming other products that meet the statutory definition of a tobacco product to be subject to chapter IX of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[4]

FDA's CTP is responsible for carrying out the Tobacco Control Act. CTP's mission is to protect Americans from tobacco-related disease and death by regulating the manufacture, distribution, and marketing of tobacco products and by educating the public, especially young people, about tobacco products and the dangers their use poses to themselves and others. CTP has several offices, including the Office of Science (OS), the Office of Health Communication and Education, and the Office of Compliance and Enforcement (OCE). OS is responsible for reviewing and evaluating PMTAs to determine whether a product is appropriate for the protection of public health. The Office of Health Communication and Education and the OCE consult with OS during their reviews.

CTP takes into account several factors when determining whether a product is appropriate for the protection of public health as provided in the FD&C Act § 910(c)(4). Among other things, CTP considers risks and benefits to the population as a whole, methods, facilities, and controls used to manufacture, process, and pack the new tobacco product, the increased or decreased likelihood that existing users of tobacco products will stop using such products, and the increased or decreased likelihood that those who do not use tobacco products will start using such products.[5] CTP independently evaluates who the likely users of the product are based on all available evidence and information contained in the application. CTP also uses external sources such as peer-reviewed articles and studies in its evaluations. CTP weighs all the potential benefits and risks from the information contained in the PMTA to make an overall determination of whether the product should be authorized for marketing.

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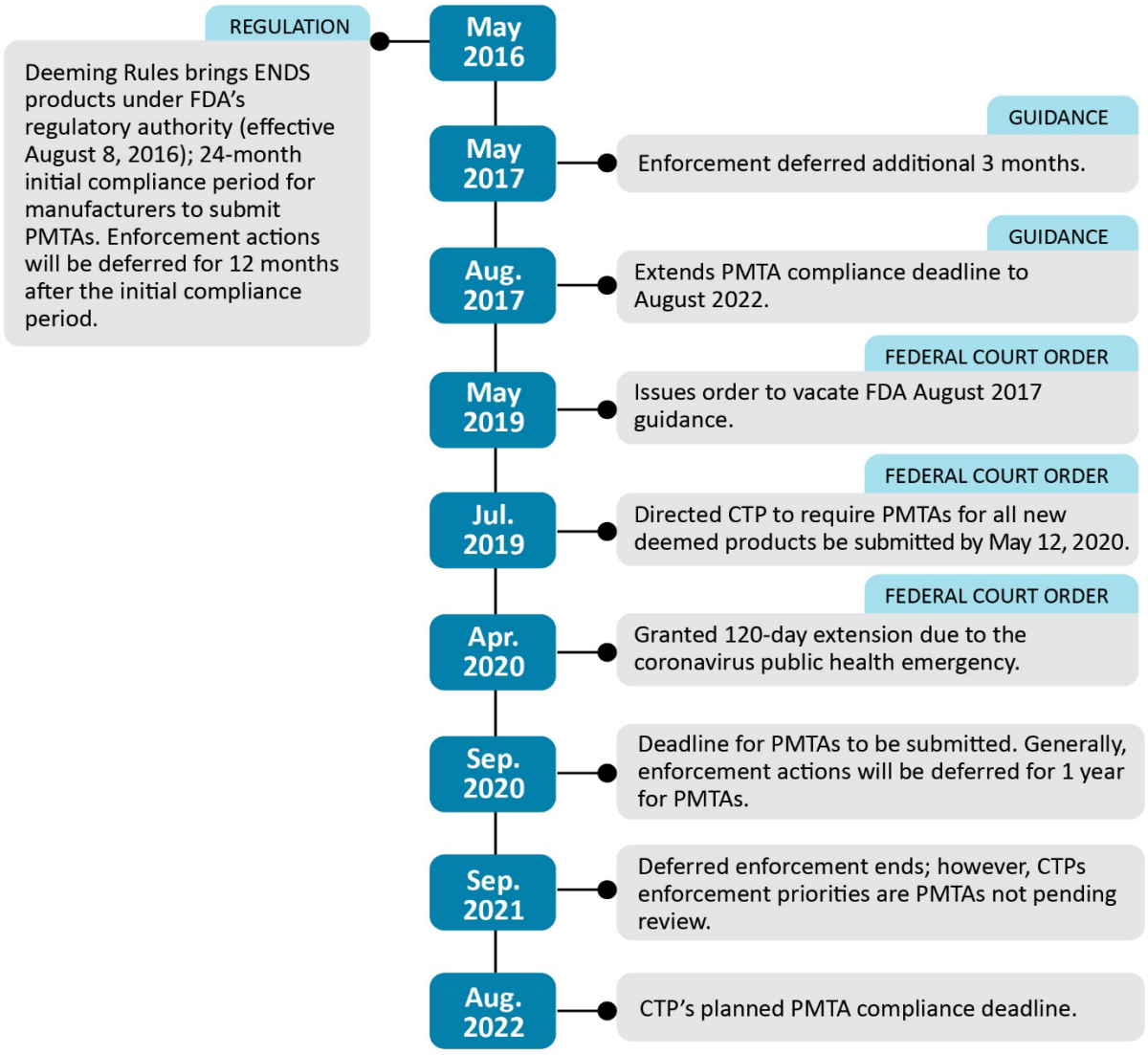
[4] FD&C Act § 901(b).

[5] Section 910 of the FD&C Act*, Application for Review of Certain Tobacco Products.* Available online at https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/section-910-federal-food-drug-and-cosmetic-act-application-review-certain-tobacco-products. Accessed on Jan. 27, 2023.

On May 10, 2016, FDA issued a final rule deeming all products that meet the statutory definition of a tobacco product, except accessories of deemed tobacco products, to be subject to FDA's tobacco product authority. This includes ENDS, cigars, pipe tobacco, waterpipe (hookah) tobacco, nicotine gels, and dissolvables that were not already subject to the FD&C Act.[6, 7] ENDS products include both the e-liquids and e-cigarettes used as ENDS, whether sold as a unit or separately. See Figure 1 for a timeline of PMTA regulation, guidance, and court orders that followed.

Figure 1: Timeline of Premarket Tobacco Application Regulation, Guidance, and Orders



[6] 81 Fed. Reg. 28974, 28976 (May 10, 2016).

[7] Vapes, vaporizers, vape pens, hookah pens, electronic cigarettes (e-cigarettes, or e-cigs), e-cigars, and e-pipes are some of the many tobacco product terms used to describe ENDS.

Premarket Tobacco Application Review Process

Under section 910 of the FD&C Act, persons wanting to market a new tobacco product must first obtain an order to do so (referred to as a "marketing order"). All deemed products that meet the definition of a new tobacco product, including ENDS, are subject to the requirements of premarket review (FD&C Act § 910(a)(2)). A premarket review of a PMTA is conducted by CTP officials and includes a scientific review to determine whether a product is appropriate for the protection of public health. Based on this determination, CTP grants or denies a marketing order for the new product.

A PMTA may be submitted by any person seeking an FDA marketing order to introduce a new tobacco product into interstate commerce. During our audit period, the applications could be submitted electronically through the CTP Portal or the FDA Electronic Submissions Gateway, or physically to CTP's Document Control Center (DCC).[8, 9] The PMTAs submitted were electronic, physical, or a combination of both. For the PMTAs submitted electronically, CTP's DCC screened the PMTA to ensure the files met security requirements and were scanned for viruses; if an issue was identified, an employee was required to access the file and determine what needed to be done to fix the issue so that the submission could move forward. For applications that were submitted on damaged, empty, or error-ridden external drives, CTP worked with its DCC to determine the next steps and identify whether the issues were CTP's or with the applicants' submission. For paper submissions, CTP used a document scanner to scan the documents and convert them into an electronic format to review. According to CTP officials, they met daily to discuss issues that were identified with the files and how to resolve them.

A PMTA must provide scientific data that demonstrates a product is appropriate for the protection of public health. To reach such a decision and to authorize marketing, FDA considers, among other things:

- risks and benefits to the population as a whole, including people who would use the proposed new tobacco product and nonusers;

- whether people who currently use any tobacco product would be more or less likely to stop using the product if the proposed new product were available;

- whether people who currently do not use any tobacco products would be more or less likely to begin using tobacco products if the new products were available; and

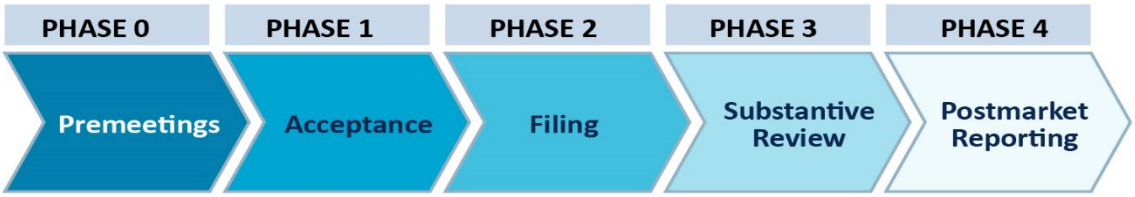
[8] The CTP Portal provides a convenient, secure online system for electronically submitting documents and receiving messages from CTP.

[9] The FDA Electronic Submissions Gateway (ESG) is an agency-wide solution for accepting electronic regulatory submissions. The FDA ESG enables the secure submission of premarket and postmarket regulatory information for review.

- the methods, facilities, and controls used to manufacture, process, and pack a new tobacco product.[10]

FDA established a five-phase PMTA review process. (See Figure 2.) Our audit focused on the three phases prior to a marketing order being granted or denied: acceptance review, filing review, and substantive review. Our audit did not include the premeeting and postmarket reporting phases because the premeeting phase is voluntary and the postmarket reporting phase does not begin until 12 months after the date of the order.[11]

Figure 2: Phases in the Premarket Tobacco Application Review Process

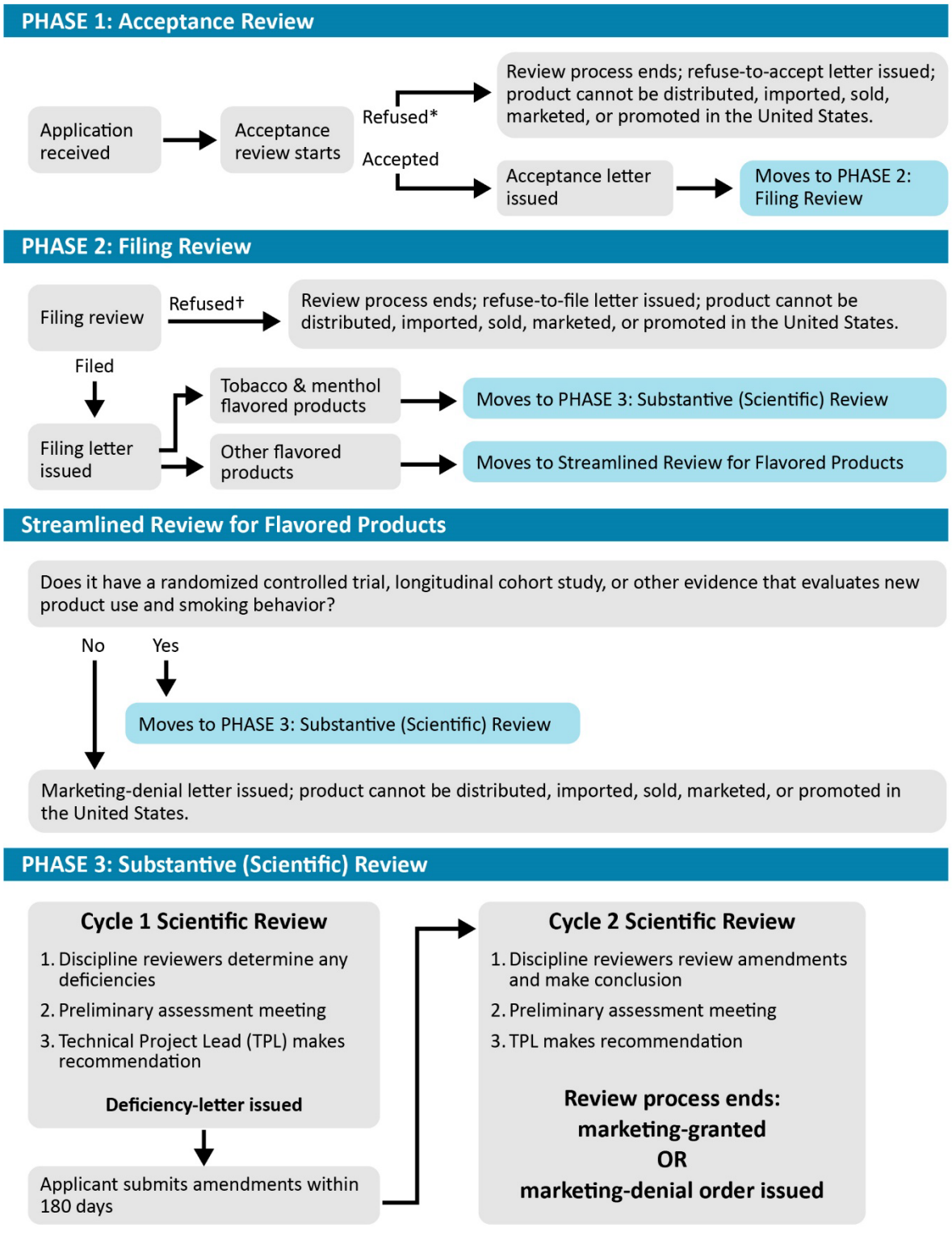


See Figure 3 on the following page for a detailed description of the PMTA review process for Phase 1 Acceptance, Phase 2 Filing, and Phase 3 Substantive Review. The PMTA review process depicted in this figure describes the general review process used during our audit period, but some PMTAs may not follow the exact process depicted. On Jan. 6, 2023, CTP officials stated that all flavored products, including menthol, are treated similarly.

[10] FD&C Act § 910(c)(4).

[11] The premeeting phase is a voluntary, presubmission formal meeting between the applicant and FDA to discuss a planned PMTA submission for a tobacco product. The outcome results in either a meeting-granted letter or meeting-denial letter. The postmarket reporting phase requires applicants to establish and maintain records and make reports that FDA requires as necessary to determine or facilitate a determination of whether there may be grounds to withdraw or temporarily suspend a marketing-granted order.

Figure 3: Premarket Tobacco Applications Review Process for Phases One, Two, and Three



* See Phase 1 "Acceptance Review" section of the report for reasons a refuse-to-accept letter may be issued.

† See Phase 2 "Filing Review" section of the report for reasons a refuse-to-file letter may be issued.

Phase 1: Acceptance Review

After a PMTA is received, it enters the acceptance review. This is an administrative review that ensures that the product falls under CTP jurisdiction and confirms that the statutory and regulatory requirements of a PMTA are met based on section 910 of the FD&C Act and the criteria set forth in 21 CFR § 1105.10–Refusal to accept a premarket submission.[12]

This phase results in either an acceptance letter or refuse-to-accept letter being sent to the applicant. If the PMTA meets any of the following conditions, a refuse-to-accept letter may be issued:

- The PMTA does not pertain to a tobacco product.
- The PMTA is not in English or does not contain complete English translations.
- If submitted electronically, the submission is in a format CTP cannot process, read, review, and archive.
- The PMTA does not contain contact information, including the applicant's name and address.
- The PMTA does not contain product-identifying information.
- The PMTA is from a foreign applicant and does not identify an authorized U.S. agent.
- The PMTA does not contain required FDA forms.
- The type of PMTA is not identified.
- The PMTA does not contain the signature of a responsible official authorized to represent an applicant.
- The PMTA does not include an environmental assessment (21 CFR § 1105.10).

If a refuse-to-accept letter is issued, the PMTA does not proceed any further in the review without the applicant resubmitting the PMTA. If an acceptance letter is issued, the PMTA proceeds to phase 2, Filing Review.

[12] In 2021, FDA finalized a final PMTA rule that describes the required content, format, and review of PMTAs. For FDA to complete a substantive review of a PMTA, the application must include the information described in the final rule (86 Fed. Reg. 55300-55439 (Oct. 5, 2021)).

Phase 2: Filing Review

The filing review is a threshold determination of whether the PMTA contains sufficient information to permit substantive review. The filing review focuses on those items within section 910(b)(1) of the FD&C Act that are immediately apparent, legally supportable, and rise to the level of being a filing review issue and not an issue for substantive scientific review. This review focuses on the presence, but not the accuracy, of such information. The result of this review is either a filing letter or a refuse-to-file letter being sent to the applicant. Per CTP, the following are potential reasons a refuse-to-file letter may be issued:

- The PMTA does not contain full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations that have been made to show the health risks of the tobacco product and whether the tobacco product presents less risk than other tobacco products.

- The PMTA does not contain a full statement of the components, ingredients, additives and properties, and the principle or principles of operation.

- The PMTA does not contain a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of the product.

- The PMTA does not include a specimen of the labeling proposed to be used for the product.

- The PMTA does not contain an adequate environmental assessment as described in 21 CFR § 25.40 or a claim of categorical exclusion under 21 CFR § 25.35.

If a refuse-to-file letter is sent, the PMTA does not proceed any further in the review process without the applicant resubmitting the PMTA. If a filing letter is sent, the PMTA proceeds to either Streamlined Flavored Product Review or phase 3, Substantive Review.

Streamlined Flavored Product Review

CTP determined that the evaluation of flavored ENDS products required robust and reliable evidence regarding the magnitude of the potential benefit to adult smokers in order to determine that marketing this type of a new tobacco product is appropriate for the protection of public health. In particular, CTP requires evidence that demonstrates the new flavored product(s) provide an added benefit to adult smokers relative to a tobacco-flavored product.

This evidence would most likely be provided through a randomized controlled trial or a longitudinal cohort study, or both.[13, 14] CTP would also consider evidence from another study design if it could reliably and robustly assess behavior change (product switching or cigarette reduction) over time, comparing users of flavored products with those of tobacco-flavored products.

On July 9, 2021, after considering the large number of applications that remained to be reviewed by the September 9, 2020, deadline, CTP decided it would conduct a streamlined review of PMTAs not in phase 3 for non-tobacco-flavored ENDS products. In a streamlined review, the reviewer examines the PMTA to identify whether it contains the necessary types of studies. The review is limited to determining the presence or absence of such studies; it does not evaluate the merits of the studies.

If the studies were present, the PMTA proceeded to phase 3. If it was determined that the application did not have the necessary types of studies, a marketing-denial-order letter was issued, and the applicant did not get the chance to correct any deficiencies. During our audit period, CTP issued denial orders for more than 1.2 million flavored products.

Phase 3: Substantive Review

Phase three is a substantive evaluation of the scientific information and cross-referenced content in a PMTA, as well as potential considerations from the Tobacco Products Scientific Advisory Committee if a PMTA is referred to it.[15]

Once a PMTA enters substantive review, a technical project lead (TPL) from OS is assigned within CTP. The TPL assembles a multidisciplinary review team comprising members from various scientific disciplines. Types of disciplines may include regulatory, engineering, chemistry, microbiology, behavioral and clinical pharmacology, toxicology, medical, epidemiology, social science, and environmental science. The TPL may also receive consultation reviews from statisticians, Office of Health Communication and Education, OCE, and the Tobacco Product Surveillance Team.

[13] A randomized controlled trial is a clinical investigation or a clinical study in which a human subject(s) is prospectively and randomly assigned to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on behavioral, biomedical, or health-related outcomes.

[14] A longitudinal cohort study is an observational study in which human subjects from a defined population are examined prospectively over time to assess an outcome or set of outcomes among study groups defined by a common characteristic (e.g., smoking cessation among users of flavored ENDS compared with users of tobacco-flavored ENDS).

[15] The Tobacco Products Scientific Advisory Committee reviews and evaluates safety, dependence, and health issues relating to tobacco products and provides appropriate advice, information, and recommendations to the Commissioner of Food and Drugs.

The substantive review phase consists of two cycles. During cycle 1, the necessary scientific disciplines are identified. The scientific disciplines evaluate information included in the PMTA and associated Tobacco Product Master Files, if referenced in the PMTA. A secondary discipline reviewer ensures clarity, comprehensiveness, and consistency with current discipline thinking. Additionally, if it is determined that inspections of the manufacturers are necessary, inspections are conducted. Once all evaluations are conducted, a cycle 1 preliminary assessment meeting is held to discuss deficiencies identified by the disciplines. At the end of cycle 1, any deficiencies found within the multidisciplinary review are sent to the applicant in a deficiency letter. The applicant generally has up to 180 days to submit amendments to the PMTA to correct the deficiencies.

Once amendments are received from the applicant, the PMTA enters cycle 2 of the substantive review process. In cycle 2, a discipline reviewer reviews the amendments to determine whether they satisfy the deficiencies. A secondary discipline reviewer ensures clarity, comprehensiveness, and consistency with current discipline thinking. Once all reviews are conducted, a preliminary assessment meeting is held to determine whether the amendments are responsive to the deficiencies. Next, the TPL reviews all the discipline reviews to ensure clarity, comprehensiveness, and consistency with OS policy and to determine whether the product is appropriate for the protection of public health. The TPL also determines whether policy issues necessitate a review by the Office of Chief Counsel and, upon request, provides written or oral briefing materials to Office of the Center Director, Office of Health Communication and Education, and OCE. The TPL review goes through additional clearance before being finalized. After the discipline and TPL reviews are finalized, either a marketing-granted order or a marketing-denial order is issued for a PMTA as a result of this review phase.

Deadline for Action on a Premarket Tobacco Application

Federal regulations require an action as promptly as possible, but not later than 180 days after the receipt of an application (FD&C Act § 910(c)(1)(A)). CTP received a majority of the PMTAs during our audit period just prior to the September 9, 2020, deadline. From September 1 through September 9, 2020, CTP received 1,959 of the 2,151 PMTAs in our audit period, which included more than 6.6 million of the 6.7 million products. Because CTP received PMTAs for millions of products within a short period of time and reviewing those within the 180-day timeframe was believed to be almost impossible, CTP decided to start the 180-day statutory deadline once a PMTA started phase 3 of the review process.

Postmarket Requirements

Applicants that receive a marketing-granted order are required to establish and maintain records and make reports that CTP requires as necessary to determine or facilitate a determination of whether there may be grounds to withdraw or temporarily suspend a marketing-granted order (21 CFR § 1114.41).

Enforcement Actions

CTP takes a three-pronged approach to help industry comply with the law by (1) developing and providing compliance training and education; (2) monitoring a regulated industry's compliance with the law through surveillance, inspections, and investigations; and (3) taking enforcement action when necessary. Enforcement actions include warning letters, civil monetary penalty complaints, no-tobacco-sale order complaints and seizures, injunctions, and criminal prosecutions.

HOW WE CONDUCTED THIS AUDIT

Our audit covered the PMTAs submitted to CTP from August 1, 2019, through September 9, 2020. To conduct our audit, we reviewed applicable Federal and program requirements related to CTP's PMTA process. We interviewed CTP officials to gain an understanding of the PMTA review process and requested and reviewed CTP's policies and procedures regarding the PMTA process.

To determine the progress CTP has made on reviewing PMTAs for ENDS products, CTP provided a list of PMTAs, along with their current status, that were received for ENDS products during our audit period. We reviewed the list to determine CTP's progress on reviewing PMTAs for ENDS products.

To determine whether CTP followed Federal statutes, regulations, policies, and guidance when granting or denying marketing orders for ENDS products, we selected a judgmental sample of 20 PMTAs. An applicant may bundle multiple products into a single PMTA submission; therefore, we judgmentally selected 38 products to review from the 20 PMTAs. Of the 38 products, 15 received a marketing-granted order, 8 received a refuse-to-accept letter, 10 received a refuse-to-file letter, and 5 received a marketing denial order. We requested and received from CTP documents submitted by the applicants for the PMTAs and the FDA work products from CTP's review of the PMTAs. We did not evaluate any scientific findings; we ensured only that reviews were completed.

To determine what actions CTP has taken to ensure that ENDS products that are not appropriate for the protection of public health are kept off the market, we conducted interviews with CTP officials to determine what enforcement actions have been taken regarding PMTAs for ENDS products.

We conducted this performance audit in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Appendix A contains the details of our audit scope and methodology.

FINDINGS

FDA's CTP made progress in reviewing PMTAs for ENDS products submitted by September 9, 2020. However, CTP was unable to complete a review of all the submitted PMTAs within the 1-year period during which products with applications filed in a timely manner might remain on the market pending CTP review. As of October 19, 2022, CTP had yet to decide on 53,128 of nearly 6.7 million products for which it received an application by the September 9, 2020, deadline.

CTP generally followed Federal statutes, regulations, policies and procedures, and guidance when granting or denying marketing orders for ENDS products; however, for the 15 products OIG reviewed that received a marketing-granted order, CTP did not issue an order within 180 days. Even though CTP had outlined a timeline to meet the 180-day deadline, it encountered delays and was unable to comply.

CTP conducted enforcement actions, such as sending warning letters and seeking injunctions, to ensure that ENDS products that were not appropriate for the protection of public health were not marketed. CTP prioritized enforcement for ENDS products for which a PMTA was not submitted by the September 9, 2020, deadline. CTP also focused on enforcement efforts for products with PMTAs that received a refuse-to-accept, refuse-to-file, or marketing-denial order letter.

THE CENTER FOR TOBACCO PRODUCTS MADE PROGRESS ON THE REVIEW OF PREMARKET TOBACCO APPLICATIONS

Under section 910 of the FD&C Act, persons wanting to market a new tobacco product (one that was not commercially marketed in the United States as of February 15, 2007, or any modified tobacco product that was commercially marketed after February 15, 2007) must first obtain a marketing order to do so under section 910(c)(1)(A)(i).

CTP made progress in reviewing PMTAs for ENDS products submitted by September 9, 2020. Between August 1, 2019, and September 9, 2020 (audit period), CTP received 2,151 submissions for PMTAs that included 6,677,152 ENDS products. As of October 19, 2022, CTP had issued marketing-granted orders for 23 ENDS products. CTP had yet to decide on 53,128 products associated with 449 submissions of PMTAs for which it received by the September 9, 2020, deadline. Table 1 on the next page represents the status as of October 19, 2022, for the products for which CTP received a PMTA during our audit period.

Table 1: Status of ENDS Products Included in Premarket Tobacco Applications Received During the Audit Period

Status of Product	Number of Products
Cancelled[*]	80,265
Refuse to Accept	221,646
Refuse to File	5,091,129
Denied	1,230,298
Granted	23[†]
Withdrawn[ǂ]	663
Pending	53,128
Total Products	**6,677,152**

[*] "Cancelled" indicates that CTP did not decide on the PMTA because there was an error, and the PMTA should not have been opened.

[†] At the time of our initial sample selection, CTP had granted 15 marketing-granted orders. Since our initial sample selection, CTP has granted an additional eight marketing-granted orders.

[ǂ] "Withdrawn" indicates that CTP acknowledged and complied with the applicant's request to remove its PMTA from consideration for a marketing order.

An applicant may bundle multiple products into a single PMTA submission. Each PMTA submission is assigned a submission tracking number (STN). During the review process, CTP may separate the products into different bundles under a single STN. The bundles can be in different phases of the review process or may have received different types of decisions. Because an STN may have multiple products with different statuses, we summarized the data according to the status of the products.

As of October 19, 2022, CTP still had not issued a decision on PMTAs for more than 50,000 products received before the September 9, 2020, deadline because CTP struggled to hire and maintain staff, which has affected its ability to process PMTAs in a timely manner. Table 2 represents the hiring gains and losses for OS within CTP from FY 2019 through FY 2022.

Table 2: Office of Science Hiring Gains and Losses

	Beginning Full-time Equivalent Staff	Full-time Equivalent Staff Gains	Full-time Equivalent Staff Losses	Ending Full-time Equivalent Staff
Fiscal Year 2019	338	33	41	330
Fiscal Year 2020 – Direct Hire Authority	330	160	27	463
Fiscal Year 2021 – Direct Hire Authority	463	131	51	543
Fiscal Year 2022	543	62	61	544

CTP officials stated that CTP has had a tremendous workload for the past couple of years and that it is not fully staffed for scientific positions. In September of 2020, CTP's OS had a goal of 700 full-time equivalent (FTE) staff to be achieved by March 2022. During FYs 2020 and 2021, the Office of Personnel Management (OPM) granted CTP direct-hire authority to fill scientific positions. During this period, CTP had a net gain of 213 FTE staff. Before the direct-hire authority, CTP's OS had a net loss of eight FTE staff in fiscal year 2019. After the direct-hire authority expired, CTP had a net gain of only one FTE staff member in fiscal year 2022. As of September 30, 2022, CTP's OS had a total of 544 FTE staff, or 156 FTE staff below its goal. CTP officials stated that having the direct hiring authority was extremely beneficial and made the process of hiring for the scientific positions more streamlined. In July of 2023, CTP's OS officials stated that its goal was to have 650 FTE staff by September 30, 2023, and 700 FTE staff by September 30, 2024. CTP officials further stated that they continue to staff scientific positions and are trying to retain the staff they have.

After the September 9, 2020, deadline, CTP continued to receive a substantial number of PMTAs for ENDS products (Table 3).

Table 3: Premarket Tobacco Applications Received After September 9, 2020

Date Application Received by FDA	Number of Products
September 10–30, 2020	1,336,713
October 1, 2020–September 30, 2021	17,362,568*
October 1, 2021–September 30, 2022	1,210,151*
Total	**19,909,432**

*Number of products as of June 30, 2023.

In April 2022, a new Federal law went into effect clarifying the FDA's authority to regulate tobacco products containing nicotine from any source, including non-tobacco nicotine.[16] As a result of this new law, FDA received many PMTAs. As additional PMTAs are received, CTP's backlog of PMTAs continues to grow.

WHILE THE CENTER FOR TOBACCO PRODUCTS GENERALLY FOLLOWED POLICIES AND PROCEDURES, IT WAS UNABLE TO ISSUE DECISIONS ON PREMARKET TOBACCO APPLICATIONS WITHIN THE REQUIRED TIMEFRAME

Under section 910(c)(1)(A) of the FD&C Act, CTP is required to issue an order that the new product may be introduced or delivered for introduction into interstate commerce as promptly as possible, but not later than 180 days after the receipt of an application.

[16] Consolidated Appropriations Act 2022, P.L. No. 117-103 (enacted Mar. 15, 2022).

CTP generally followed Federal statutes, regulations, policies and procedures, and guidance when granting or denying marketing orders for ENDS products. However, for the 15 products with a marketing order granted that we reviewed, CTP did not issue a decision within the 180-day deadline from the start of phase 3 review. Instead, CTP took from 483 to 633 days to conduct a phase 3 substantive review on these products. See Table 4 for more information on the substantive review timelines for the three manufacturers that received marketing orders for the 15 ENDS products in our judgmental sample.

Table 4: Phase 3 Substantive Review Times

	MFR 1	MFR 2	MFR 3
Cycle 1 Kickoff Date	12/2/2019	3/30/2020	10/19/2019
Deficiency Letter*	5/19/2020	7/29/2020	6/26/2020
Number of Days in Cycle 1	169	121	251
Cycle 2 Kickoff Date	12/2/2020	11/30/2020	3/17/2021
Marketing-Granted Order Letter†	10/12/2021	4/26/2022	3/24/2022
Number of Days in Cycle 2	314	512	372
Total Number of Cycle Days	**483**	**633**	**623**

* A deficiency letter indicates additional information is needed to complete the scientific review.

† A marketing-granted order letter is required to legally market a new tobacco product in the United States.

The extended substantive reviews occurred because the court ruling moved up the deadline for receipt of PMTAs; therefore, CTP received PMTAs for approximately 6.7 million ENDS products, the majority of which were submitted within a week of the court-ordered deadline. CTP officials stated that they had significantly less time than expected to prepare for the high volume and concurrent, rather than rolling, submission of applications. Additionally, CTP officials stated that because CTP had received so many applications at once, they knew they would not be able to meet the 180-day requirement. Therefore, CTP determined that the 180-day deadline would not begin until an application was complete or entered the phase 3 substantive review.[17] Additionally, during the phase 3 substantive review process, if CTP issued a deficiency letter after the cycle 1 review, CTP paused tracking the time until it began the cycle 2 review. Our assessment of the PMTA timeline for our sampled items is based on CTP's determination that the 180 days begins with the phase 3 substantive review process.

CTP created a set of review tools and standardized templates to enhance the quality and consistency of scientific discipline and TPL reviews. Additionally, CTP conducted a pilot study before the September 9, 2020, deadline to test new processes with a shortened scientific review timeline of 40 calendar days. One of the PMTAs in our sample was included in the pilot

[17] For PMTAs received after our audit period, CTP began tracking the 180-day requirement when the PMTA entered acceptance review.

study. To review the PMTA in our sample, CTP assigned 14 primary reviewers with 4 of the scientific disciplines assigned more than 1 primary reviewer. Some reviewers had previous experience with performing reviews of substantial equivalence tobacco products or PMTA reviews of different types of products.[18]

Most of the reviewers were unable to complete their review within the 40 calendar days timeline required by the pilot. For those reviewers who did complete the review within the timeline, some had previous experience with PMTA reviews. However, overall, all reviewers expressed concern with the limited review time of 40 days. Reviewers expressed concern that there was too little time for application review and drafting due to the intense pace of work, depth of thinking required during the review, and the amount of additional work outside of PMTA review.

Before and during our audit period, CTP conducted pilot studies and revised its procedures in attempts to improve the PMTA review process. In another attempt to improve the PMTA review process, on July 19, 2022, FDA Commissioner Robert Califf requested that the Reagan-Udall Foundation convene an Independent Expert Panel (Panel) to conduct an evaluation of CTP with the aim of addressing immediate issues and providing recommendations to position CTP for greater success in the future. The Panel convened to evaluate and provide recommendations to FDA in four primary areas: regulations and guidance, application review, compliance and enforcement, and communication with the public and other stakeholders. The report was issued in December of 2022, and CTP is tracking its actions in response to the Panel's recommendations.[19, 20]

Regarding the substantive review phase taking longer than the 180-day timeline, CTP stated that because these were generally precedent-setting decisions, all scientific and legal issues had to be carefully considered, which took additional time that may not be required as CTP gains additional experience with ENDS PMTA reviews. ENDS products included in PMTAs submitted by the September 9, 2020, deadline for which CTP has not issued a negative action may continue to be on the market and available to the public without a determination that they are appropriate for the protection of public health.

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[18] A substantially equivalent tobacco product is one that has been found by CTP to have either the same characteristics as a tobacco product that is commercially marketed (predicate product) or has different characteristics from the predicate product, but the substantial equivalence report demonstrates that the new product does not raise different questions of public health.

[19] Reagan-Udall Foundation, "Operational Evaluation of Certain Components of FDA's Tobacco Program." Available online at Operational Evaluation of Certain Components of FDA's Tobacco Program Dec. 2022.pdf (reaganudall.org). Accessed on Mar. 14, 2023.

[20] FDA, "Actions to Address Recommendations from the Reagan-Udall Evaluation of CTP." Available online at https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp/actions-address-recommendations-reagan-udall-evaluation-ctp. Accessed on Apr. 21, 2023.

THE CENTER FOR TOBACCO PRODUCTS CONDUCTED ENFORCEMENT ACTIONS RELATED TO ELECTRONIC NICOTINE DELIVERY SYSTEMS PRODUCTS

CTP has broad authority under the Tobacco Control Act to regulate the sale and marketing of tobacco products, including ENDS products. CTP's potential enforcement tools for ENDS product manufacturers include advisory actions (e.g., warning letters), administrative actions (e.g., civil monetary penalties), and judicial actions (e.g., seizure, injunction, or criminal prosecution). Generally, if ENDS products do not have an FDA marketing order that complies with section 910(c)(1)(A)(i) of the FD&C Act, those products are considered adulterated under section 902(6)(A). Those products are also considered misbranded under section 903(a)(6) of the FD&C Act because a notice or other information respecting these products was not provided as required by section 905(j) of the FD&C Act.

CTP conducted enforcement actions to ensure that ENDS products that were not appropriate for the protection of public health were not marketed. During our audit period, CTP prioritized enforcement actions related to products that did not have CTP authorization to be marketed. These products fell into two categories: (1) non-submitter, which is a company that did not submit a PMTA for its deemed product by the deadline of September 9, 2020, and (2) negative action enforcement, which is for products that have received a marketing-denial order, refuse-to-file letter, or refuse-to-accept letter. As of July 12, 2023, CTP's highest priority for enforcement involve those products for which no PMTA was submitted and ENDS products that received a negative action. In addition, unauthorized ENDS products with high market share and or those that are popular with youth are a high enforcement priority.

After the September 9, 2020, deadline for PMTAs to be submitted, OCE officials stated that OCE had obtained a list of companies that had submitted a PMTA and compared that list with FDA's list of companies that were domestically registered to manufacture tobacco products. After identifying the companies that had not submitted a PMTA, OCE officials stated that OCE had determined whether the companies maintained an online presence and prioritized a review to gather evidence to support issuing a warning letter to the company. For those companies without an online presence or those that OCE did not find sufficient evidence to support issuing a warning letter, OCE officials stated that OCE would follow up with an inspection.

In September of 2021, the first marketing-denial orders were issued. OCE officials stated that OCE had used the same process outlined for non-submitters to determine whether companies were in compliance after receiving a marketing-denial order. As of October 2022, more than 440 warning letters were issued to firms marketing illegal e-cigarettes containing tobacco-derived nicotine. According to OCE officials, most companies generally want to work with OCE when they are notified of noncompliance and generally try to comply after receiving a warning letter.

On October 18, 2022, the Department of Justice, on FDA's behalf, filed the first complaints for permanent injunctions in Federal district courts against six e-cigarette manufacturers that failed to submit PMTAs for their products and have continued to illegally manufacture, sell, and

distribute their products.[21] The injunctions, if granted, would require the companies to stop manufacturing, selling, and distributing their e-cigarettes.[22] Additionally, the injunctions, if granted, would require the companies to obtain a marketing order before marketing the products, as required by law.

RECOMMENDATIONS

We recommend that the Center for Tobacco Products:

- work with OPM to obtain direct-hire authority to assist CTP in reaching its FTE goal and

- assess the PMTA review process and develop an action plan to resolve the backlog of PMTA applications and achieve compliance with the 180-day statutory timeline.

FOOD AND DRUG ADMINISTRATION COMMENTS

In its written comments on our draft report and commenting on behalf of CTP, FDA concurred with the two recommendations. In response to our recommendations, FDA stated that:

- HHS, on behalf of CTP, submitted a new request to OPM for direct-hire authority. If granted, this request will fund primarily scientific positions, which contribute to and support the tobacco product review program. As of September 2023, the request remains pending with OPM.

- It will develop an action plan to resolve the backlog of applications, which will identify opportunities to improve review efficiency, program coordination and communication, and stakeholder engagement. It has begun work on the action plan and is committed to providing updates to the public on a regular basis, including as a part of routine updates on progress to address the Reagan-Udall evaluation recommendations. This work will be ongoing and is not expected to have an end date.

FDA also provided technical comments on our draft report which we addressed as appropriate. FDA's comments, excluding technical comments, are included as Appendix B.

[21] FDA, "FDA, DOJ Seek Permanent Injunctions Against Six E-Cigarette Manufacturers." Available online at https://www.fda.gov/news-events/press-announcements/fda-doj-seek-permanent-injunctions-against-six-e-cigarette-manufacturers. Accessed on Apr. 21, 2023.

[22] Consent decrees and or permanent injunctions were filed and entered against five of the e-cigarette manufacturers as of the end of our fieldwork.

APPENDIX A: AUDIT SCOPE AND METHODOLOGY

SCOPE

Our audit period was from August 1, 2019, through September 9, 2020. To determine CTP's progress on reviewing applications for ENDS products, we requested data on the PMTAs received during our audit period and analyzed the data to determine the number of applications received and their status as of October 19, 2022.

To determine whether CTP followed Federal statutes, regulations, policies, and guidance when granting or denying ENDS products, we reviewed CTP's policies and procedures and developed checklists using Federal statutes and regulations. We used the checklists to determine whether CTP granted or denied those products following Federal statutes and regulations. To determine what actions CTP has taken to ensure that ENDS products that are not appropriate for the protection of public health are not marketed, we interviewed CTP officials in OCE.

We obtained a list of all the PMTAs submitted during our audit period along with their current status and then chose a judgmental sample of 20 PMTAs. Of the 20 PMTAs, 15 were associated with a product that had received a marketing-granted order. The other 5 PMTAs had products within them that had received a refuse-to-accept letter, refuse-to-file letter, or a marketing-denial order. Then, we chose a judgmental sample of 38 products from the 20 PMTAs. Of the 38 products, 15 products received a marketing-granted order, 8 products received a refuse-to-accept letter, 10 products received a refuse-to-file letter, and 5 products received a marketing-denial order.

We assessed CTP's design, implementation, and operating effectiveness of internal controls over the PMTA review process by reviewing CTP's internal policies and procedures and internal memos regarding changes in the process.

We conducted our audit from October 2021 through December 2022.

METHODOLOGY

To accomplish our objective, we:

- reviewed applicable Federal and program requirements related to CTP's PMTA process;
- interviewed CTP officials regarding the status of applications they received, CTP's PMTA review process, and any enforcement actions taken;
- requested and analyzed data on the PMTAs received during our audit period;
- requested and reviewed CTP's policies and procedures regarding the PMTA process;

- developed a checklist for each phase of the PMTA review process;

- selected a judgmental sample of 20 PMTAs, ensuring that products within the PMTAs had achieved the varying stages of the PMTA review process or had received a marketing-granted order;

- requested and received the PMTA submission and CTP work products for the PMTAs selected;

- selected a judgmental sample of products from each of the 20 PMTAs, ensuring inclusion of the various types of products;

- reviewed the submission documents and CTP work products corresponding to those products; and

- discussed the results of our audit with CTP officials.

We conducted this performance audit in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

APPENDIX B: FOOD AND DRUG ADMINISTRATION COMMENTS

DATE: September 13, 2023

TO: Amy J. Frontz
Deputy Inspector General of Audit Services
Office of the Inspector General

FROM: Beethika Khan
Associate Commissioner for Economics and Analysis
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

Beethika Khan -S
Digitally signed by Beethika Khan -S
Date: 2023.09.13 13:40:26 -04'00'

SUBJECT: Draft Report, A-06-22-01002

Attached are the Food and Drug Administration's general and technical comments to the Office of Inspector General's August 11, 2023 draft report entitled *The Food and Drug Administration Needs to Improve the Premarket Tobacco Application Review Process for Electronic Nicotine Delivery Systems to Protect Public Health*. Thank you for the opportunity to provide feedback.

Attachments

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

FDA's General Comments

OIG Draft Report: The Food and Drug Administration Needs To Improve the Premarket Tobacco Application Review Process for Electronic Nicotine Delivery Systems To Protect Public Health, A-06-22-01002

FDA appreciates the opportunity to review and comment on OIG's draft report.

Premarket review of new tobacco products is a critical part of the FDA's Center for Tobacco Products' (CTP) work to protect the public, especially youth, from the harms associated with tobacco product use. Before introducing a new tobacco product[1] to the U.S. market, a company must submit a marketing application to the FDA and receive authorization. Applicants submitting a premarket tobacco product application (PMTA) must demonstrate that the marketing of the new tobacco product would be "appropriate for the protection of the public health."[2] In order to reach such a decision and to authorize marketing, FDA considers the risks and benefits to the population as a whole, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products, as well as the increased or decreased likelihood that those who do not use tobacco products will start using such products.[3] Review of a PMTA is a collaborative process that typically includes reviewers from a wide variety of scientific disciplines including microbiology, chemistry, engineering, behavioral and clinical pharmacology, social science, medicine, toxicology, epidemiology, and environmental science.

Since FDA's "Deeming Rule"[4] took effect in 2016, e-cigarettes and all other electronic nicotine delivery systems (ENDS) have been required to obtain FDA authorization to be legally marketed. Under a federal court order, applications for deemed new tobacco products that were already on the market when the Deeming Rule took effect were required to be submitted to FDA by September 9, 2020.[5]

FDA took a number of actions to prepare for the expected large number of PMTAs. These efforts included improving information technology systems, engaging with stakeholders, significantly increasing hiring, and streamlining review procedures. To assist manufacturers and importers preparing applications, FDA published several foundational rules and guidances related to the

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[1] Section 910(a)(1) of the Federal Food, Drug, and Cosmetic Act defines "new tobacco product" to mean: (A) any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007; or (B) any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007.

[2] Section 910(c)(4) of the Federal Food, Drug, and Cosmetic Act.

[3] Section 910(c)(4) of the Federal Food, Drug, and Cosmetic Act; ***see also*** https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/premarket-tobacco-product-applications.

[4] https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/deeming-tobacco-products-be-subject-federal-food-drug-and-cosmetic-act-amended-family-smoking.

[5] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-court-grants-fdas-request-extension-premarket-review-submission-deadline.

application process. In 2018 and 2019, FDA held public meetings on the application review process to provide information about the review process and to answer questions.

In total, FDA received nearly 26 million applications, including nearly 6.7 million applications by the September 9, 2020, deadline. Applications for more than 19 million more products were submitted after the deadline. To date, FDA has made determinations on more than 99% of all of these applications, including authorizing 23 new e-cigarette products and devices, and issuing refuse to accept letters, refuse to file letters, or marketing denial orders for millions of products.

CTP is committed to continuously strengthening the PMTA review process, working internally and through engagement with external stakeholders to communicate on scientific issues and practices to support efficiency, effectiveness and transparency; hire additional staff to enhance program management and implementation, and shorten review times; and increase internal communication to improve scientific engagement and deliberation.

FDA's responses to OIG's specific recommendations are below.

Work with the Office of Personnel Management to obtain direct-hire authority to assist CTP in reaching its FTE goal.

FDA concurs with this recommendation. In the past, Direct Hire Appointment Authority (DHA) has allowed CTP to increase staffing and efficiencies. FDA's initial request for DHA was for three years (through September 30, 2022) to allow FDA to recruit the appropriate talent. In October 2019, CTP was granted DHA for a period of two years, for scientific and technical positions such as Health Science, Toxicologist, Social Scientist, Pharmacologist, Information Technology Specialist, and Microbiologist, which are key in reviewing applications. During those two years, CTP was able to increase its staff by nearly 38%, from 785 to 1,082. Since its expiration, CTP has seen a decrease in the ability to hire; thus, reaching staffing levels needed to review pending and new premarket applications has been a challenge.

In April 2023, HHS, on behalf of CTP, submitted a new request to the Office of Personnel Management (OPM) for DHA. If granted, this request will fund primarily scientific positions, which contribute to and support the tobacco product review program. As of September 2023, the request remains pending with OPM.

Assess the PMTA review process and develop an action plan to resolve the backlog of PMTA applications and achieve compliance with the 180-day statutory timeline.

FDA concurs with this recommendation. Since receiving the many millions of applications starting in September 2020, FDA has assessed and made improvements to its PMTA processes to inform application prioritization, review and clearance processes, and program improvement and sustainability.

In 2022, the FDA Commissioner requested that the Reagan-Udall Foundation facilitate an external operational evaluation of CTP. The evaluation offered a total of 15 recommendations

related to regulatory processes and agency operations. FDA is committed to addressing all of the recommendations, including those related to application review.

FDA will develop an action plan to resolve the backlog of applications, which will identify opportunities to improve review efficiency, program coordination and communication, and stakeholder engagement.

Action plan components may include, but will not be limited to:

- Explore streamlined review opportunities to improve speed and efficiency.
- Improve and/or leverage IT systems and databases to more efficiently process, ingest, and triage applications.
- Hire additional, dedicated personnel to enhance program management and implementation, including a PMTA Coordinator, who will develop and refine program priorities, set goals, develop and implement action plans, and coordinate communication across the office.
- Engage with external stakeholders to better communicate on scientific issues and practices to support efficiency and effectiveness. For example, CTP will hold a public meeting in October 2023 to discuss the PMTA process and solicit stakeholder input.
- Resume posting of scientific policy memos and reviewers' guides, as appropriate.

CTP has begun work on the action plan, and is committed to providing updates to the public on a regular basis, including as a part of routine updates on progress to address the Reagan-Udall evaluation recommendations. This work will be ongoing and is not expected to have an end date.